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10/527,694	11/01/2005	Tetsushi Taguchi	052203	7280

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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,694	TAGUCHI ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,7 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6,7 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 12 May 2008 in which claims 1, 5 and 8-10 were cancelled, claims 4, 6, 7 and 11 are amended to change the scope and breadth of the claims, and new claims 12 and 13 are added.

Claims 4, 6, 7 and 11-13 are currently pending and are examined on the merits herein.

This application is a National Stage entry of PCT/JP03/11669 filed on 1 November 2005 and claims priority to foreign application Japan 2002-265982 filed on 11 September 2002. A certified copy of the foreign priority document in Japanese is received.

Rejections Withdrawn

In view of the cancellation of claims 1, 5 and 8-10, all rejections made with respect to claims 1, 5 and 8-10 in the previous Office Action are withdrawn.

Applicants' amendment, filed on 12 May 2008, deleting the phrase "derivative" from claims 4, 6, 7 and 11, overcomes the rejection made in the previous Office Action of claim 4, 6 and 7 under 35 USC § 112, second paragraph.

This rejection has thus been **withdrawn**.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 12 May 2008, wherein the limitations in pending claims 4 and 11 as amended now have been changed, claims 6 and 7 depend from claim 4, and new claims 12 and 13 are added. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 12 February 2008, have been modified and are listed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: steps for using the crosslinked high-molecular-weight product. In the absence of any steps, one would be unable to carry out the method for using the high-molecular-weight product as intended by the Applicants.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[Section 0001]

Claims 4, 6, 7 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000-212286 by Nagura *et al.* (of record) in view of Hermanson (chapter 3, entitled “Zero-Length Cross-Linkers", PTO-892, Ref. U).

Nagura *et al.* discloses a biodegradable gelatin gel (Section 0002) that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages. Polycarboxylic acids included in the invention are, but not limited to, malonic acid, fumaric acid, succinic acid, adipic acid, citric acid, tartaric acid and malic acid. Nagura *et al.* further teaches that the gel is not limited to crosslinking with gelatin, but also includes water-soluble proteins such as water-soluble polysaccharides (such as chitosan, alginic acid and chondroitin sulfate) and collagen. Nagura *et al.* discloses that the gelatin gel is considered a biodegradable biomaterial that can be used as an artificial skin, wound dressing material, and a cell culture based material (Section 0008).

Nagura *et al.* does not teach polycarboxylic acids that are modified in at least one carboxyl group with N-hydroxysuccinimide or N-hydroxysulfosuccinimide.

Hermanson teaches zero-length crosslinkers that mediate the conjugation of two molecules by forming a bond containing no additional atoms. Zero-length crosslinking agents eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct linkage between the two substances (p. 169, paragraph 1). Carbodiimides, such as EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride), are the most popular type of zero-length crosslinkers in use, being efficient in forming conjugates between two protein molecules, between a peptide and a protein, between oligonucleotides and proteins, or any combination of these with small molecules (p. 169, last paragraph). N-hydroxysulfosuccinimide (sulfo-NHS) are hydrophilic active groups that react rapidly with amines on target molecules (p. 173, first full paragraph). Figure 108 provides a schematic of the reaction (p. 175). In the presence of EDC, sulfo-NHS modifies the carboxylic acid group of a molecule/protein to form a sulfo-NHS activated intermediate. In the presence of amine nucleophiles that can attack at the carbonyl group of the NHS-ester, the sulfo-NHS group rapidly leaves, creating a stable amide linkage with the amine (p. 173, first full paragraph). The advantage of adding sulfo-NHS to EDC reactions is to increase the stability of the active intermediate, which ultimately reacts with the attacking amine (p. 173, second full paragraph). EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, last paragraph).

A general protocol for the conjugation of a protein to a molecule (i.e. small molecule, peptide, another protein, etc.) is provided (p. 174-176). The protein to be modified is dissolved in 0.1 M sodium phosphate, pH 7.4 at a concentration of 1-10 mg/mL (p. 174, step 1). The molecule to be coupled is also dissolved in 0.1 M sodium phosphate, pH 7.4 (p. 175, step 2) and then added to a solution of the protein in at least a 10-fold molar excess over the amount of protein present (particular important when the conjugation is to a small molecule) (p. 175, step 3). EDC is then added to the

protein/molecule solution to obtain a 10-fold molar excess of EDC to the protein (p. 175, step 4). Alternatively, a 0.05-0.1 M EDC concentration would also work well. Sulfo-NHS, at a final concentration of 5 mM, is then added to the reaction (p. 175, step 4) which is allowed to proceed for 2 h at room temperature (p. 176, step 5) before purification of the conjugate by gel filtration or dialysis (p. 176, step 6).

It is noted that the references do not explicitly indicate that the gelatin gel biomaterial is metabolized in vivo. However, since the gelatin gel claimed by Applicant is the same as that disclosed by Nagura *et al.*, it is inherent that the gelatin gel biomaterial disclosed by Nagura *et al.* can also be metabolized in vivo. When, as here, the prior art appears to contain the exact same compound and Applicant's own disclosure supports the suitability of the prior art composition as the inventive compound, the burden is on the Applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

It is noted that the references do not explicitly teach the reaction conditions as indicated in the limitations of claim 11. However, it is considered well within the capabilities of one of ordinary skill in the art to optimize the reaction conditions to provide optimal conditions for the conjugation reaction. See below for recitation of section from MPEP § 2144.05. Furthermore, the protocol as disclosed by Hermanson provides for a range of workable conditions.

The following is a recitation from MPEP § 2144.05:

> A. Optimization Within Prior Art Conditions or Through Routine Experimentation
> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning a biodegradable gelatin gel that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages, with the teachings of Hermanson, regarding the mediation of the conjugation between a protein and a molecule with sufo-NHS/EDC. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that zero-length crosslinking agents (such as sulfo-NHS and EDC) eliminate the potential for crossreactivity between two substances to be coupled together by mediating a direct linkage between the two substances (p. 169, paragraph 1). Moreover, Hermanson further teaches that EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation over that obtained solely with EDC (p. 173, last paragraph).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed on 12 May 2008 have been considered but are moot in view of the new ground(s) of rejection above. Additionally it is noted that Applicants argue that Nagura *et al.* do not disclose or suggest modifying malic acid, oxalacetic acid, citric acid or *cis*-aconitic acid with N-hydroxysuccinimide or N-hydroxysulfosuccinimide. However, Hermanson, relied upon as the secondary

reference in the new ground(s) of rejection here teaches the N-hydroxysulfosuccinimide modification of small molecules with N-hydroxysuccinimide or N-hydroxysulfosuccinimide that is not expressly disclosed by Nagura *et al.*

Thus, the claimed invention is obvious over the combined teachings of the prior art.

[Section 0002]

Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2000-212286 by Nagura *et al.* (of record) in view of Hermanson (chapter 3, entitled "Zero-Length Cross-Linkers," PTO-892, Ref. U) as applied to claims 4, 6, 7 and 11 above, and further in view of US Patent No. 6,166,130 to Rhee *et al.* (herein referred to as the '130 patent, of record).

The teachings of Nagura *et al.* and Hermanson were as described above in the claim rejections under 35 USC § 103. The references do not teach a method for using the crosslinked high-molecular-weight product as indicated in the claim limitations of claims 12 and 13.

The Rhee '130 patent teaches methods for using crosslinked polymer compositions to effect adhesion between a first surface and a second surface. The crosslinked composition can include proteins such as collagen and derivatives of various naturally occurring polysaccharides, such as glycosylaminoglycans (column 11, line 38 and claims 11-13). Rhee *et al.* further teaches methods for using the crosslinked polymer compositions as bioadhesives (abstract and column 17, line 15) to effect tissue

augmentation (abstract and line 16), to inhibit the formation of surgical adhesions (abstract and column 19, line 53), to coat a surface of a synthetic implant (abstract and column 20, line 20), to treat aneurism (column 20, line 53), and to deliver biologically active agents (column 15, line 32).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nagura *et al.*, concerning a biodegradable gelatin gel that is obtained by adding a polycarboxylic acid to gelatin and heating it to introduce chemical crosslinkages, with the teachings of Hermanson, regarding the mediation of the conjugation between a protein and a molecule with sufo-NHS/EDC, with the teachings of the Rhee '130 patent, regarding methods for using crosslinked polymer compositions to effect adhesion between a first surface and a second surface. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Nagura *et al.*, that the obtained polymer gel film is both biodegradable and biocompatible and thus useful for medical applications.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed on 12 May 2008 have been considered but are moot in view of the new ground(s) of rejection above. Additionally it is noted that Applicants argue that Nagura *et al.* do not disclose or suggest modifying malic acid, oxalacetic acid, citric acid or *cis*-aconitic acid with N-hydroxysuccinimide or N-

hydroxysulfosuccinimide. However, Hermanson, relied upon as the secondary reference in the new ground(s) of rejection here teaches the N-hydroxysulfosuccinimide modification of small molecules with N-hydroxysuccinimide or N-hydroxysulfosuccinimide that is not expressly disclosed by Nagura *et al.*

Thus, the claimed invention is obvious over the combined teachings of the prior art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
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/SCARLETT GOON/
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